

ability to attribute the effects observed to the intervention itself. Fifth, and perhaps most important, the authors did not disclose the name of the KO/salmon-oil blend they used, nor its manufacturer. On the basis of the compositional data given in the article, the fatty acid composition of the KO/salmon-oil product does not match that of either the KO identification criteria in the US Pharmacopeia–National Formulary or our experience with hundreds of batches of KO analyzed at Aker BioMarine (Table 1). Consequently, the product tested cannot have been composed of 88% native Antarctic KO, and their conclusions should not have been associated with KO. Given the multiple and fundamental problems with this study, it is unfortunate that it was published in its present form.

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## Reply to N Hoem

Dear Editor:

Hoem's comments on our study are misguided, as detailed below. We also note that he is a krill industry scientist, who therefore has a clear conflict of interest.

Our study conclusions were based on a gold-standard trial design, that is, a double-blind, randomized controlled crossover trial (1). Importantly, we also presented the results of an independent analysis of the trial oil, because recent studies showed that the accuracy of package labeling is frequently poor (2, 3).

Hoem is misguided when stating that the treatment difference (14%;  $P = 0.049$ ) is "relatively small." For example, metformin (the first-line treatment of type 2 diabetes) improved insulin sensitivity by 17% in a group of sedentary overweight nonpatients with diabetes (4). Thus, the 14% difference we observed is relevant.

Contrary to what Hoem suggests, our recommendations are not made lightly, and we have emphasized the need for further studies. However, we note that omega-3-rich oils are commonly recommended to lower cardiovascular disease risk in healthy and at-risk groups. The evidence that n-3 PUFA-rich oils reduce cardiovascular disease risk is poor, with systematic reviews showing that marine oils are ineffective (5, 6). In addition, insulin sensitivity is of central importance in the pathogenesis of cardiovascular disease (7). In this context, our study showing that a krill–salmon-oil blend lowers

insulin sensitivity is of concern, because long-term treatment with this oil might increase the risk of cardiovascular disease. Given our data and the lack of evidence for benefit in those at increased cardiovascular disease risk, we believe it is responsible to caution against the use of similar oils in this population. As stated, further studies are needed to determine the chemical component or components that led to these adverse effects, which could potentially allow the production of oils without these effects. We have carefully discussed the known chemical components of this oil, and although we believe it is likely to relate to the krill component, we emphasized that this could not be determined by our study.

With regard to Hoem's second comment, mixed models (including baseline as a covariate) are highly appropriate to analyze our data from a crossover trial [e.g., Brown and Prescott (8)]. Our statistical models were entirely adequate, and the "specific elements" were clearly described in our article.

Hoem's third comment shows that he has misunderstood our findings, which are summarized below:

- 1) A negative effect of the krill–salmon oil on insulin sensitivity was identified as per preplanned analysis of this primary outcome, while accounting for the baseline values.
- 2) Because this finding was entirely unexpected (we hypothesized the exact opposite would occur), we conducted a mediation analysis to evaluate whether our findings were associated with the n-3 PUFAs or with other chemical components of the oil. This mediation analysis showed no change in insulin sensitivity (compared with baseline) with the control oil ( $P = 0.88$ ) but a Matsuda index decrease of  $-1.31$  ( $\sim 24\%$ ) after taking the krill–salmon oil ( $P = 0.0008$ ).
- 3) Furthermore, when within-treatment differences were assessed in post hoc analyses, there was no significant change in insulin sensitivity from baseline with the control oil ( $P = 0.23$ ), but participants experienced a decrease in the Matsuda index of  $-0.98$  ( $\sim 18\%$ ;  $P = 0.002$ ) while taking krill–salmon oil.

Thus, there was good evidence of an adverse effect of krill–salmon oil on insulin sensitivity.

Nonetheless, Hoem is correct that, at baseline, there was a positive association between the omega-3 index and insulin sensitivity (9), a finding also reported by other authors (10). But we note that controlling for the omega-3 index would have been equally appropriate if there had been a negative correlation between omega-3 index and insulin sensitivity. In showing that the negative effect was stronger after adjustment for the omega-3 index in the mediation analysis, it suggests that the adverse effect is unlikely to be due to n-3 PUFAs. No further conclusions can be drawn from that analysis.

As we concluded in our article, current randomized controlled trial evidence is simply insufficient to determine whether supplemental n-3 PUFAs can improve insulin sensitivity in humans. The Akinkuolie et al. (11) meta-analysis referred to by Hoem showed a small positive effect of n-3 PUFA supplementation on insulin sensitivity only in studies reporting HOMA-IR, but no overall effect. However, this meta-analysis collated 11 highly heterogeneous trials with wide variation in dose, study populations, and design.

Hoem's assertion that our study was unblinded is incorrect, because it was indeed a double-blind randomized controlled trial. Unlike the vast majority of trials on n-3 PUFA-rich oils, we objectively assessed blinding. The index used indicated that blinding was unsuccessful, but our study was not open-label at all. Although 24 of 47 participants correctly guessed their final treatment, 23 were incorrect or unsure. We believe that this level of unblinding is



probably common, given that marine oils are associated with “fishy” eructations. Furthermore, investigators involved in assessments, laboratory work, and statistical analysis remained blinded. Of note, because the primary outcome was an objective laboratory test, it would be unlikely to be affected by unblinding.

Finally, the method used by Hoem to calculate fatty acid content in mg/g appears to be flawed. It is incorrect to convert the percentage area on the gas chromatogram to quantitative composition by multiplication with a single constant for all fatty acids. The krill–salmon oil in our study was manufactured by Nutrizel Ltd., and this is clearly stated in Methods (1). The information from the manufacturer indicated 88% krill and 12% salmon oil, with a percentage abundance of n-3 PUFAs of 27.7%, which was similar to our independent analysis (31.2%). The actual n-3 PUFA content was determined by gas chromatography by using calibration curves derived from an authentic fatty acid mixture (1). Hoem has erroneously assumed that krill oil composition is constant among products. For example, a study recently reported the fatty acid composition of a krill oil (12), which was different from both ours and Hoem’s oil. The composition of oil derived from fish varies across seasons (13) and location of catch (14), making such variation in krill oil unsurprising. We are confident that our study was robust, and we believe that both our conclusions and recommendations are justified.

The authors had no financial or nonfinancial conflicts of interest to disclose that may be relevant to this work. The funder of the original trial (Douglas Charitable Trust) had no role in its design, data collection and analysis, decision to publish, or preparation of the article; in addition, the funder had no role in the preparation of this letter.

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